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Original Investigation

Phenotypic Manifestation of Genetic Risk for Schizophrenia During Adolescence in the General Population

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IMPORTANCE Schizophrenia is a highly heritable, polygenic condition characterized by a relatively diverse phenotype and frequent comorbid conditions, such as anxiety and depression. At present, limited evidence explains how genetic risk for schizophrenia is manifest in the general population.

OBJECTIVE To investigate the extent to which genetic risk for schizophrenia is associated with different phenotypes during adolescence in a population-based birth cohort.

DESIGN, SETTING, AND PARTICIPANTS This cohort study used data from the Avon Longitudinal Study of Parents and Children (ALSPAC). Of 14 062 children in the birth cohort, genetic data were available for 9912 adolescents. Data were collected periodically from September 6, 1990, and collection is ongoing. Data were analyzed from March 4 to August 13, 2015.

EXPOSURES Polygenic risk scores (PRSs) for schizophrenia generated for individuals in the ALSPAC cohort using results of the second Psychiatric Genomics Consortium Schizophrenia genome-wide association study as a training set.

MAIN OUTCOMES AND MEASURES Logistic regression was used to assess associations between the schizophrenia PRS and (1) psychotic experiences (Psychosis-Like Symptom Interview at 12 and 18 years of age), (2) negative symptoms (Community Assessment of Psychic Experiences at 16.5 years of age), (3) depressive disorder (Development and Well-Being Assessment at 15.5 years of age), and (4) anxiety disorder (Development and Well-Being Assessment at 15.5 years of age) in adolescence.

RESULTS Of the 8230 ALSPAC participants whose genetic data passed quality control checks (51.2% male, 48.8% female), 3676 to 5444 participated in assessments from 12 to 18 years of age. The PRSs created using single-nucleotide polymorphisms with a training-set $P \leq .05$ threshold were associated with negative symptoms (odds ratio [OR] per SD increase in PRS, 1.21; 95% CI, 1.08-1.36; R^2 = 0.007) and anxiety disorder (OR per SD increase in PRS, 1.17; 95% CI, 1.06- 1.29; R^2 = 0.005). No evidence was found of an association between schizophrenia PRS and psychotic experiences (OR per SD increase in PRS, 1.08; 95% CI, 0.98-1.19; R^2 = 0.001) or depressive disorder (OR per SD increase in PRS, 1.02; 95% CI, 0.91-1.13; R^2 = 0.00005). Results were mostly consistent across different training-set P value thresholds and using different cutoffs and measures of the psychopathological outcomes.

CONCLUSIONS AND RELEVANCE This study demonstrates polygenic overlaps between common genetic polymorphisms associated with schizophrenia and negative symptoms and anxiety disorder but not with psychotic experiences or depression. Because the genetic risk for schizophrenia appears to be manifest as anxiety and negative symptoms during adolescence, a greater focus on these phenotypes rather than on psychotic experiences might be required for prediction of transition in at-risk samples.

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Editorial

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Schizophrenia has a heritability of approximately 80%, and genome-wide association studies (GWASs) indicate that multiple independent loci contribute to its etiology.[1] The importance of studying the phenotypic manifestations of increased genetic liability for schizophrenia has been long recognized and originally involved small samples of individuals at high risk as indexed by having a family history.[2] Genetic advances now provide the opportunity to extend the power and generalizability of high-risk studies into the general population by examining individuals according to genetic risk. Although individual loci have small effects on risk, multiple-loci approaches show that, cumulatively, alleles on current GWAS platforms explain one-half to one-third of the genetic risk for schizophrenia.[3,4] Information from even moderately associated alleles can be collapsed into a single polygenic risk score (PRS) that can be used to explore shared genetic effects with other disorders and to examine how genetic risk is manifest early during development.[5]

Schizophrenia is defined by psychotic experiences (hallucinations, delusions, and thought disorder) and negative symptoms (eg, blunted affect and apathy), although cognitive deficits are also common as is comorbidity with other diagnoses, particularly affective and anxiety disorders.[6] Longitudinal studies show that anxiety, depression, and cognitive deficits often predate schizophrenia,[7-11] indicating that these phenotypes might represent early expression of genetic risk for schizophrenia. Although genetic overlap across psychiatric disorders is common,[12-15] knowledge of how genetic risk is expressed at different stages of the life course could foster understanding of the etiologic mechanisms and risk prediction and inform targeted interventions.

Three previous studies[16-18] have used a schizophrenia PRS generated from a GWAS training set that captured approximately 3% of the proportion of risk variance[4] to examine associations with symptoms that characterize schizophrenia. In the first study,[16] the schizophrenia PRS was not associated with symptom dimensions characteristic of the disorder in cases with schizophrenia or control individuals (while associations within the whole sample were attributed to confounding by case-control status). Similarly, another study[17] reported no association with positive symptom, cognitive, and negative symptom dimensions in a general population sample of adolescents. Finally, the third study[18] found no strong evidence that the schizophrenia PRS was associated with psychotic experiences at 12 years of age within the population-based Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort. Subsequently, a larger GWAS[1] has been completed that explains a much greater proportion of risk variance, thus providing greater power to examine how genetic risk is manifest during development.[19] We aimed to examine the psychopathological features associated with the early expression of genetic risk for schizophrenia and, more specifically, whether a schizophrenia PRS derived from the most recent GWAS is associated with (1) psychotic experiences, (2) negative symptoms, (3) anxiety disorders, or (4) depression during adolescence in a large population-based sample.

Methods

Participants

The sample consisted of young individuals within the ALSPAC cohort. The initial cohort consisted of 14 062 children born to women residing in the former Avon Health Authority area with an expected delivery date from April 1, 1991, to December 31, 1992 (http://www.bristol.ac.uk/alspac/; all available data are given at http://www.bristol.ac.uk/alspac/researchers/access/).[20,21] Data were collected periodically from September 6, 1990, and collection is ongoing. Ethical approval for the study was obtained from the ALSPAC Law and Ethics Committee and the local research ethics committees (listed at http://www.bristol.ac.uk/alspac/researchers/research-ethics/). All participants provided written informed consent.

Genetic Data

Genetic data were acquired from 9912 participants using a genome-wide single-nucleotide polymorphism (SNP) genotyping platform (HumanHap550-Quad; Illumina). After quality control assessment, imputation, and restriction to 1 adolescent per family, genetic data were available for 8230 individuals (more detail is found in the eMethods in the Supplement).

Measures

Psychotic Experiences

The semistructured Psychosis-Like Symptom Interview[22,23] was used to assess psychotic experiences (hallucinations, delusions, or experiences of thought interference) at ages 12 and 18 years. To maximize the numbers within our sample, individuals were deemed to have a psychotic experience if rated as having 1 or more definite psychotic experiences at 12 or 18 years of age compared with no experiences or suspected psychotic experiences only at 12 or 18 years of age. More details on the Psychosis-Like Symptom Interview and on the other outcome measures used in this study are given in the eMethods in the Supplement.

Negative Symptoms

Negative symptoms were assessed using 10 questions based on items from the Community Assessment of Psychic Experiences self-report questionnaire[24] at 16.5 years of age (eMethods and eTable 1 in the Supplement). The questions measure negative symptoms, such as apathy, anergia, and asociality. Each item was rated on a 4-point scale (0 indicates never; 1, sometimes; 2, often; and 3, always). A total score was constructed based on the sum of responses (minimum score, 0; maximum score, 30). A binary variable was created using a total score of 14 as a cutoff that was chosen to define approximately the top decile (9.18%) of the sample.

Depressive and Anxiety Disorders

Depressive and anxiety disorder outcomes were derived from the semistructured Development and Well-Being Assessment interview at 15.5 years of age. The interview is a valid in-

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Table 1. Individuals With Outcome Measure[a]

Age, y	Data Source	Outcome Measure	Binary Outcome Measure Type	All Participants No.	All Participants Outcome, No. (%)	Genotyped Participants No.	Genotyped Participants Outcome, No. (%)
12	PLIKSI	Psychotic experiences	Yes or no	6792	383 (5.64)	5103	280 (5.49)
18	PLIKSI	Psychotic experiences	Yes or no	4718	229 (4.85)	3486	168 (4.82)
12 and 18[b]	PLIKSI	Psychotic experiences	Yes or no	7452	575 (7.72)	5444	419 (7.70)
16.5	CAPE	Negative symptoms	Score <14 or ≥14[c]	5095	467 (9.17)	3673	337 (9.18)
15.5	DAWBA[d]	Depression	<15% or ≥15% likelihood	5365	498 (9.28)	4106	373 (9.08)
15.5	DAWBA[d]	Anxiety	<15% or ≥15% likelihood	5367	596 (11.10)	4107	444 (10.81)

Abbreviations: CAPE, Community Assessment of Psychic Experiences; DAWBA, Development and Well-Being Assessment; PLIKSI, Psychosis-Like Symptom Interview.

[a] Includes psychotic experiences, negative symptoms, depression, and anxiety.

[b] Indicates individuals who completed at least 1 interview session at 12 and/or 18 years of age.

[c] Total scores range from 0 to 30, with higher scores indicating worse symptoms.

[d] An individual within the 15% band category has a 15% likelihood of having a depressive or anxiety disorder. Higher percentage categories indicate a higher chance of having a depressive or anxiety disorder.

strument in community and clinical samples.[25] *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* and *DSM-IV* diagnoses of depressive or any anxiety disorder were generated using a computerized diagnostic algorithm that predicts the likelihood of a clinical diagnostic rating (more information is available at http://www.DAWBA.com).[26]

We defined individuals as having a depressive disorder or an anxiety disorder if they were categorized in the Development and Well-Being Assessment band predicting at least a 15% probability of clinical diagnosis, a cutoff selected to define the approximate top deciles of the sample. We conducted a series of sensitivity analyses using different phenotype score cutoffs to define binary outcomes and using different measures where available to test the robustness of our findings (eMethods in the Supplement).

Polygenic Risk Score

Construction of the PRS follows the methods described by the International Schizophrenia Consortium.[4] The PRS was constructed using results from the second Psychiatric Genomics Consortium (PGC) schizophrenia GWAS (eMethods in the Supplement).[1] Polygenic scores were calculated for each ALSPAC individual using the PLINK (version 1.07) score command.[27] Scores were created by summing the number of risk alleles present for each SNP (0, 1, or 2) weighted by the logarithm of its odds ratio (OR) for schizophrenia from the PGC.

Our primary analysis used scores generated from a list of SNPs with a GWAS training-set $P \leq .05$ threshold, which is the threshold that maximally captures schizophrenia liability.[1] Because the composition of a PRS is a balance between true and null effects,[28] scores generated using lists of SNPs meeting a series of P value thresholds and using all independent SNPs meeting genome-wide significance as reported by the PGC schizophrenia GWAS[1] were used in sensitivity analyses.

Statistical Analysis

Data were analyzed from March 4 to August 13, 2015. We used logistic regression to test the association between outcomes and the schizophrenia PRS. Results are presented as ORs and 95% CIs per SD increase in PRS. Nagelkerke R^2 values are also presented as a measure of variance explained. Nonlinear associations between the PRS and outcomes were examined by inclusion of quadratic terms. We examined whether associations with our outcomes were independent by inclusion of all phenotypes within a multivariable model. To correct for multiple testing arising from using different P value thresholds within our sensitivity analyses, we computed permutation-adjusted P values (eMethods in the Supplement).

To test whether the effect size of the schizophrenia PRS was the same or different across phenotypes, we used bivariate probit regression to model pairs of outcomes jointly. We tested equality of regression parameters expressing the effect of the schizophrenia PRS (threshold $P = .05$) on each outcome using a likelihood ratio test to compare a model that allows effect estimates to differ with a model where the PRS effect was constrained to be equal for both outcomes.[29,30] All statistical analyses were performed using STATA statistical software (version 13; StataCorp LP).

Results

Associations Between Schizophrenia PRS and Psychopathological Outcomes

The numbers of individuals who participated in the Psychosis-Like Symptom Interview at 12 and 18 years of age or completed questions relating to negative symptoms at 16.5 years of age and depression and anxiety at 15.5 years of age are shown in **Table 1**. Of 8230 ALSPAC adolescents whose genetic data passed quality control checks (51.2% male and 48.8% female), 3676 to 5444 participated in assessments from 12 to 18 years of age.

We found no strong evidence that individuals who had a higher PRS, and thus increased genetic risk for schizophrenia, had an increased risk for developing psychotic experiences (OR per SD increase in PRS, 1.08; 95% CI, 0.98-1.19; permutation-adjusted $P = .14$; $R^2 = 0.001$) (**Figure**, A, and eTable 2 in the Supplement).

We observed strong evidence of an association between the schizophrenia PRS and negative symptoms at 16.5 years of age (OR, 1.21; 95% CI, 1.08-1.36; permutation-adjusted

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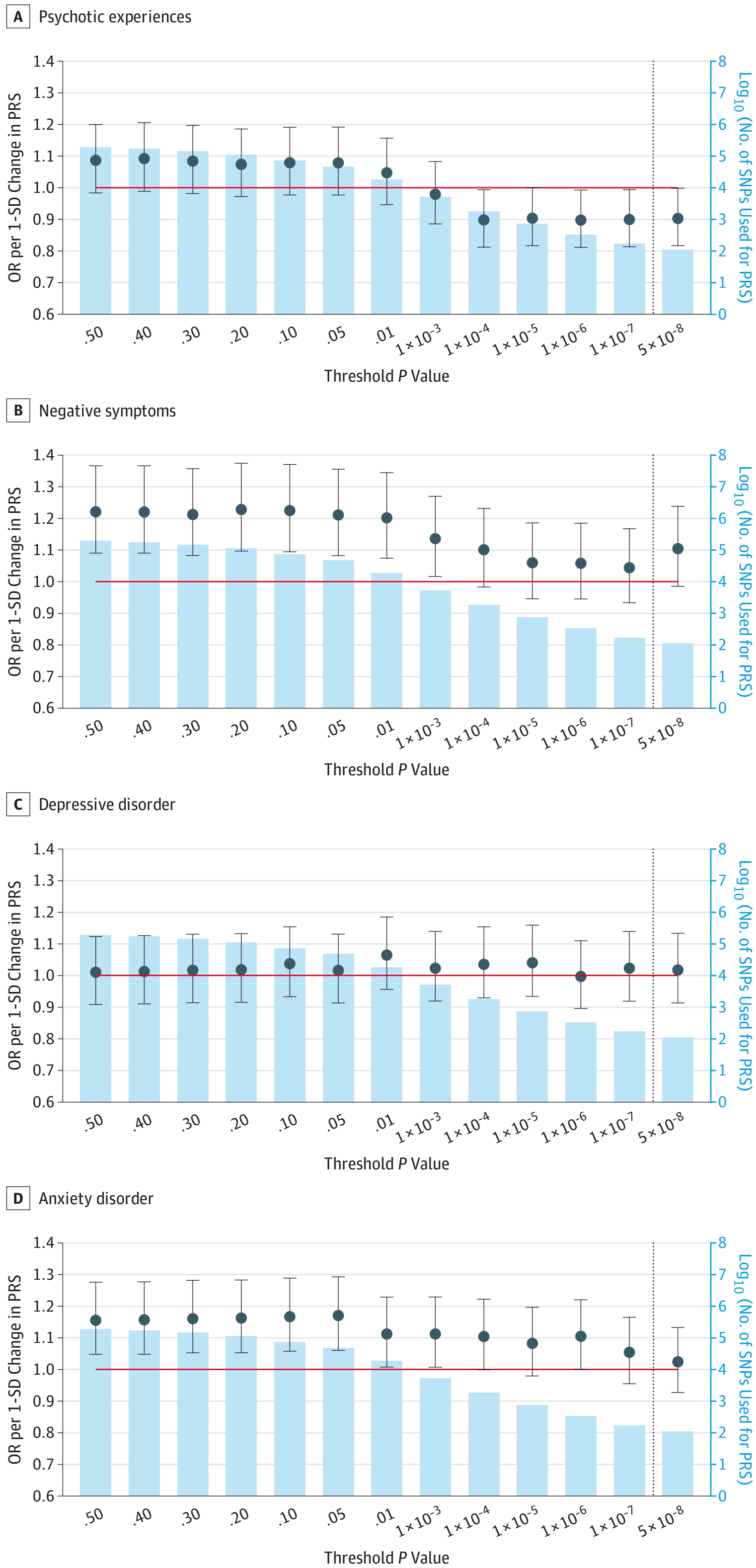
Figure. Associations Between Polygenic Risk Scores (PRSs) for Schizophrenia and Phenotypes



Odds ratios (ORs) per SD change in PRS for schizophrenia are shown (data markers), with upper and lower error bars indicating 95% CIs. The ORs are shown for a range of PRSs generated using lists of single-nucleotide polymorphisms (SNPs) meeting a series of P value thresholds. The bars indicate the log10 times the number of SNPs used to create the PRSs. A genome-wide significant (threshold $P = 5 \times 10^{-8}$) PRS was created from 111 genome-wide significant schizophrenia SNPs as reported by the second Psychiatric Genomics Consortium.[1] Red lines indicate the null value.

P = .001; R^2 = 0.007) (Figure, B, and eTable 2 in the Supplement). We also observed strong evidence that individuals with a higher schizophrenia PRS were at an increased risk for anxiety disorder at 15.5 years of age (OR per SD increase in poly-

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Table 2. Effects of Schizophrenia PRS on Psychopathological Outcomes and Comparison of Specific vs Common Effect[a]

Phenotype 1	Phenotype 2	No. of Participants	Effect, OR (95% CI) Phenotype Specific 1	Effect, OR (95% CI) Phenotype Specific 2	Effect, OR (95% CI) Common	P Value[b]
Psychotic experiences	Negative symptoms	3288	1.04 (0.93-1.15)	1.15 (1.04-1.26)	1.09 (1.02-1.18)	.14
Psychotic experiences	Depressive disorder	3965	1.06 (0.97-1.16)	1.02 (0.94-1.12)	1.04 (0.97-1.11)	.58
Psychotic experiences	Anxiety disorder	3966	1.05 (0.96-1.15)	1.16 (1.06-1.26)	1.11 (1.04-1.19)	.11
Negative symptoms	Depressive disorder	2872	1.17 (1.06-1.30)	0.99 (0.90-1.10)	1.08 (1.00-1.17)	.02
Negative symptoms	Anxiety disorder	2873	1.17 (1.05-1.30)	1.16 (1.05-1.28)	1.16 (1.08-1.26)	.92
Depressive disorder	Anxiety disorder	4106	1.01 (0.92-1.10)	1.14 (1.04-1.23)	1.07 (1.00-1.15)	.02

Abbreviations: OR, odds ratio; PRS, polygenic risk score.

[a] Includes complete case data using bivariate model estimation. The ORs are calculated per SD increase in PRS, with a threshold *P* = .05 for the discovery sample.

[b] Calculated from likelihood ratio tests comparing a model assuming psychopathologic-specific effect vs a common effect model when the exposure effect is constrained to be the same across phenotypes. *P* = .5, for example, would provide little evidence that the association between the PRS and phenotype 1 was different from that for the association between the PRS and phenotype 2. *P* = .01, for example, would provide strong evidence of a difference. The eMethods in the Supplement details how ORs were derived.

genic score, 1.17; 95% CI, 1.06-1.29; permutation-adjusted $P = .002$; $R^2 = 0.005$) (Figure, D, and eTable 2 in the Supplement). We found no strong evidence of an association between the PRS and depressive disorder at 15.5 years of age (OR per SD increase in polygenic score, 1.02; 95% CI, 0.91-1.13; permutation-adjusted $P = .77$; $R^2 = 0.00005$) (Figure, C, and eTable 2 in the Supplement).

We found no strong evidence to support nonlinear effects of polygenic risk on any of the phenotypes examined. Results per decile of PRS for a training-set threshold of $P = .05$ are presented in eTable 3 in the Supplement. Associations with negative symptoms and anxiety disorder were independent and persisted when testing all phenotypes within a multivariable model (eTables 4 to 7 in the Supplement).

Common and Specific Associations With Schizophrenia PRS

Tetrachoric correlations between each psychopathological outcome are shown in eTable 8 in the Supplement. The results of the bivariate analyses examining whether the schizophrenia PRS (threshold $P = .05$) effect sizes are similar or different across phenotypes are summarized in **Table 2**. We observed some evidence that the strong associations between the schizophrenia PRS and negative symptoms and anxiety are different from the association between the PRS and depression (both $P = .02$), with weaker evidence that they are different from the associations of the PRS with psychotic experiences ($P = .14$ and $P = .11$, respectively). We found no strong evidence that the association between the PRS effect and negative symptoms differed from that for anxiety ($P = .92$).

Sensitivity Analyses

Our results were unchanged when we used different cutoff values or different measurement tools to assess our outcomes (eFigures 1-5 in the Supplement), when we adjusted for parental self-reported history of schizophrenia or depression, or when we excluded individuals with a psychotic disorder at 18 years of age. Results were also consistent across all training-set *P* value thresholds for almost all outcomes. The exception was psychotic experiences, for which we found weak evidence that increased genetic risk was associated with a decreased risk of psychotic experiences at lower training-set *P* value thresholds (threshold $P \leq 1 \times 10^{-7}$; OR per SD increase in polygenic score, 0.90; 95% CI, 0.81-0.99; permutation-adjusted $P = .04$; $R^2 = 0.002$) (Figure, A, and eTable 2 in the Supplement).

Discussion

In this study, we examined how an increased genetic risk for schizophrenia is manifest phenotypically during adolescence in the general population. We found no strong evidence of an association with the occurrence of psychotic experiences or depressive disorder. However, we found strong evidence that negative symptoms and anxiety disorders were more common in adolescents with a higher genetic risk and that these risks were independent of each other.

Although the absence of an association between a genetic risk for schizophrenia and psychotic experiences in adolescence may seem surprising, these findings are consistent with those of previous studies that have examined this relationship.[17,18] The estimates of association and strength of evidence in this study are very similar to those from a previous study using ALSPAC,[18] although the power in our study is substantially greater given the use of a much larger training set to generate the risk-scoring algorithm.

At *P* value thresholds that maximally capture schizophrenia liability, psychotic experiences were more common in those with higher genetic risk, albeit the CIs included the null. At the most stringent *P* value thresholds, however, we found weak evidence that genetic risk was associated with reduced psychotic experiences. This finding could be caused by random error or could result from attrition bias. Missing data are likely greater for those who develop a psychotic disorder and for those at high genetic risk. Therefore, psychotic experiences may be underrepresented in participants with high compared with low genetic risk included in these analyses, akin to the apparently protective effect of smoking on Alzheimer disease risk seen using risk rather than rate models of analysis.[31] Why this would only be observed at *P* value thresholds that explain less of the variance for schizophrenia is not clear.

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A number of potential explanations exist for our findings of strong evidence of an association between genetic risk for schizophrenia and negative symptoms and anxiety disorder but not with psychotic experiences in the general population. First, genetic risk for schizophrenia may be expressed heterotypically during adolescence as anxiety and negative symptoms, and psychotic experiences may develop later. For the minority of individuals who later develop schizophrenia, anxiety and negative symptoms would represent prodromal symptoms of the disorder. This possibility implies that, compared with psychotic experiences arising later in life, hallucinations and paranoid beliefs arising during adolescence might be explained to a greater degree by nongenetic effects, such as childhood trauma[32,33] or cannabis use,[34] than by genetic risk for schizophrenia. The association between genetic risk for schizophrenia and psychotic experiences might therefore become stronger with increasing age akin to that seen for general cognitive ability.[35]

Anxiety and negative symptoms might occur as early manifestations of genetic risk for schizophrenia, and we might speculate on possible mechanisms. For example, disturbed biological processes secondary to genetic variation might result in subtle alterations in prediction error processing and attributional salience that might lead to anxiety before the onset of clear-cut psychotic phenomena.[36,37] Genetic risk for schizophrenia is also associated with impaired childhood performance IQ in this cohort,[38] although we do not know whether variants acting primarily through different brain pathways are differentially related to these phenotypes.

Second, genetic risk for schizophrenia may be expressed during adolescence as increased psychotic experiences, anxiety, and negative symptoms, but psychotic experiences may be observed with greater measurement error; thus, associations would be relatively underpowered for this phenotype. Use of a semistructured interview and similar estimates using questionnaires suggest that this explanation is unlikely but cannot be excluded.

Third, genetic variants identified as showing an association with schizophrenia in the GWAS may only weakly index the risk for hallucinations and delusions and may reflect genetic risk more strongly for other characteristics of the disorder, such as negative symptoms that index severity or chronicity of illness and that might be selected for in clinically ascertained samples. Similarly, such ascertainment might be biased toward those with multiple morbidities, for example, comorbid anxiety disorders. Studies that have examined symptom dimensions within schizophrenia[39] and in the general population[40,41] show that the heritability of negative and disorganized symptoms is greater than that of positive symptoms and that schizophrenia polygenic risk is more strongly associated with negative and disorganized symptoms than positive symptoms.[42]

Although evidence exists of genetic overlap between schizophrenia and major depressive disorder in adults,[12,43] we found no evidence to support this overlap in our study. Measures of depression in this study may capture more transient disorders in adolescence that obscure a genetic overlap between schizophrenia and a more persistent, chronic form of depression.

Our results indicate that anxiety and negative symptoms are likely to be the best markers of high genetic risk for schizophrenia in population-based samples; however, the variance of these phenotypes explained by schizophrenia genetic risk is small (0.5%-0.7%), and the negative symptoms measure used in the general population might not fully capture the negative symptoms seen in schizophrenia. Our findings have potentially important implications for studies of at-risk samples among whom current approaches for informing prediction of transition rely heavily on psychotic experiences. Our results are consistent with an evolving literature describing anxiety as a common symptom during the prodromal stage of psychosis.[44-46]

Our study has a number of strengths. First, we used the most recent schizophrenia GWAS from the PGC[1]—the largest schizophrenia data set available—as a training set, thus minimizing measurement error. Second, we used a large, well-characterized, relatively homogeneous, population-based sample for examining psychosis-related phenotypes during adolescence, a key period of development that closely predates the start of the peak in incidence of schizophrenia. Third, we used a semistructured interview to determine the presence of psychotic experiences, as used clinically. We also used multiple measures of depression and anxiety at different ages during adolescence and different cutoffs of these and of measures of psychotic experiences and negative symptoms as sensitivity analyses to test the robustness of our findings.

Our study also has a number of limitations. First, despite the use of one of the largest population-based birth cohorts worldwide with the required data, our sample may not be adequately powered to identify small effects of cumulative genetic risk on the phenotypes examined,[19] especially given potential differences in heritability across the phenotypes.[14,40,41] Given that our sample is too small to estimate heritability of the phenotypes accurately, determining whether the absence of evidence of association between a phenotype and genetic risk for schizophrenia reflects an absence of genetic correlation or inadequate power is difficult. Second, missing data in the cohort could lead to bias in our estimates. Genetic risk for schizophrenia[47] and presence of mental health problems are associated with reduced retention in cohort studies, which would tend to underestimate associations. Although selective missingness may have led to overestimates of association, this possibility seems unlikely for some of our phenotypes but not others. A further limitation is that rare genetic variants are not captured by a GWAS; therefore, we are only able to examine the effect of common variants (as captured by the current GWAS) on adolescent phenotype expression.

Conclusions

Our results highlight the need for GWAS consortia of schizophrenia to include detailed phenotyping data, to examine the extent to which current GWAS findings relate to specific phenotypes, and to identify genetic variants and pathways that are symptom-domain specific rather than to examine the presence of disorder per se. Furthermore, large population-based

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longitudinal studies with robust measures of these phenotypic constructs are required to determine how genetic risk for schizophrenia is expressed from childhood through adulthood and whether this expression changes with age, to examine potential mediators and moderators of risk, and to determine the usefulness of genetic risk scores for prediction of transition to psychosis. A better understanding of how genetic risk for schizophrenia manifests during development could inform early recognition of problems in those at greatest risk and potentially inform targeted interventions.

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